07-05-01 1611

CASE 4-19046/A/19689/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL279244648US	July 3, 2001
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,521,184
ISSUED May 28, 1996
INVENTOR(S) Jürg Zimmermann

FOR: PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Attached in triplicate is an Application for the extension of the term of U.S. Patent No. 5,521,184 under 35 USC § 156.

The Commissioner is hereby authorized to charge the $1,120.00 fee prescribed in 37 CFR § 1.20(j)(1), as well as any additional fees which may be necessitated in connection with the filing of this Application for Patent Extension to Deposit Account No. 19-0134 in the name of Novartis Corporation. Two additional copies of this transmittal letter are being submitted for charging papers.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6921

Joseph J. Borovian
Agent for Applicant
Reg. No. 26,631

5521184

JJB:bks

Attachs.: Application for Patent Extension (incl. Appendices A-G) (3)
Two additional copies of this transmittal letter
Postcard

Date: July 3, 2001

07/03/2001 AZERGAUI 00000041 190134
1120.00 CH

CASE 4-19046/A/19689/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL279244648US — Express Mail Label Number

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,521,184

ISSUED May 28, 1996

INVENTOR(S) Jürg Zimmermann

FOR: PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Box Patent Ext.
Assistant Commissioner for Patents
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TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Attached in triplicate is an Application for the extension of the term of U.S. Patent No. 5,521,184 under 35 USC § 156.

The Commissioner is hereby authorized to charge the $1,120.00 fee prescribed in 37 CFR § 1.20(j)(1), as well as any additional fees which may be necessitated in connection with the filing of this Application for Patent Extension to Deposit Account No. 19-0134 in the name of Novartis Corporation. Two additional copies of this transmittal letter are being submitted for charging papers.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6921

Joseph J. Borovian
Agent for Applicant
Reg. No. 26,631

JJB:bks

Attachs.: Application for Patent Extension (incl. Appendices A-G) (3)
Two additional copies of this transmittal letter
Postcard

Date: July 3, 2001

CASE 4-19046/A/19689/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL279244648US	July 3, 2001
Express Mail Label Number	Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,521,184

ISSUED: MAY 28, 1996

INVENTOR: JÜRG ZIMMERMAN

FOR: PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Assistant Commissioner for Patents
Washington, D.C. 20231

PATENT TERM EXTENSION APPLICATION UNDER 35 USC §156

Sir:

Pursuant to 35 USC §156 and 37 CFR §1.710 *et seq.*, Novartis Corporation ("Applicant"), a Corporation of the State of New York, hereby requests an extension of the patent term due to regulatory review of U.S. Patent No. 5,521,184, which was granted on May 28, 1996.

Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 5,521,184 by virtue of an assignment from the inventor, Jürg Zimmerman, to Ciba-Geigy Corporation, which later changed its name to Novartis Corporation. This assignment is recorded in the U.S. Patent and Trademark Office at Reel 7767, Frame 0596. A Certificate of Change of Name certifying the change of name from Ciba-Geigy Corporation to Novartis Corporation was submitted for recordation in the U.S. Patent and Trademark Office concurrently herewith. Copies of each of these documents evidencing that title to U.S. Patent No. 5,521,184 is vested in Novartis Corporation are attached hereto as Appendix A.

An originally executed Power of Attorney evidencing that the undersigned is an agent authorized to act on behalf of Novartis Corporation is attached hereto as Appendix B.

In accordance with 35 USC §156 and 37 CFR § 1.710-1.785, especially §1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analagously to 37 CFR §1.740.

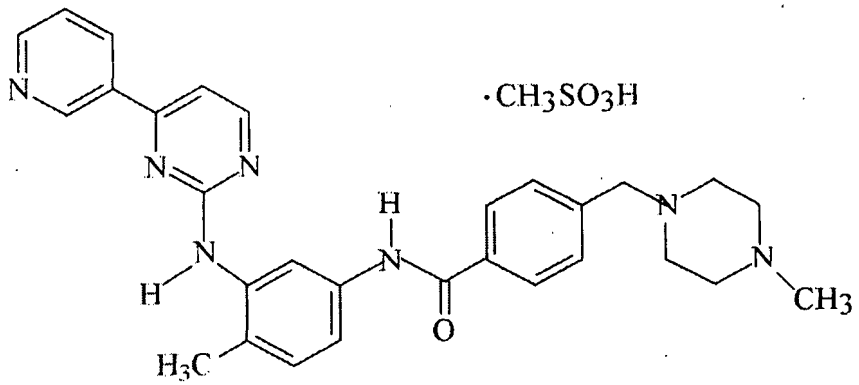
(1) Identification of the Approved Product

(a) Chemical Name: benzamide, 4-[(4-methyl-l-piperazinyl)methyl]-N-[4-methyl-3-[4-(3-pyridinyl)-2-pyrimidinyl]aminophenyl]-, methanesulfonate salt; also known as N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methyl-phenyl}-4-(3-pyridyl)-2-pyrimidine-amine, methanesulfonate salt.

(b) Tradename: GLEEVEC™

(c) USAN Name: Imatinib mesylate

(d) Chemical Structure:



(2) Identification of Federal Statute Under Which Regulatory Review Occurred

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (21 USC §355).

(3) Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing on May 10, 2001.

(4) Active Ingredient Statement

The sole active ingredient in GLEEVEC™ is imatinib mesylate. Imatinib, or any salt thereof, including imatinib mesylate, had not previously been approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act

prior to the approval of NDA 21-335 under the Federal Food, Drug and Cosmetic Act on May 10, 2001.

(5) Statement of Timely Filing of This Request

The last day on which this application could be submitted is July 9, 2001, which is 60 days after the approval of NDA 21-335 on May 10, 2001. This application is timely filed on or prior to July 9, 2001.

(6) Identification of Patent for Which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 5,521,184, which issued on May 28, 1996, to Jürg Zimmerman, the term of which would otherwise expire on May 28, 2013.

(7) Copy of U.S. Patent No. 5,521,184

A complete copy of U.S. Patent No. 5,521,184 is attached as Appendix C.

(8) Post Issuance Activity

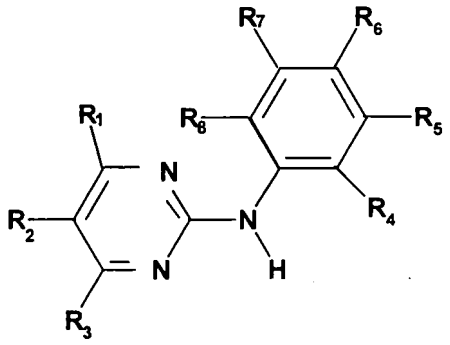
No Certificate of Correction, Terminal Disclaimer, Reexamination Certificate or Reissue has been issued or requested with respect to U.S. Patent No. 5,521,184. The first maintenance fee for U.S. Patent No. 5,521,184 in the amount of $940.00 was paid on November 2, 1999 and debited to Applicant's Deposit Account on November 20, 1999. A copy of the receipt for the maintenance fee payment is attached as Appendix D.

(9) Statement Showing How the Claims of the Patent for Which Extension is Sought Cover the Approved Product

The operative claims in question are Claims 1-5, 10-13, and 21-23. Each of Claims 1-5, 10-13 and 23 claim a compound or compounds which include the approved product, imatinib mesylate. Claim 21 claims a composition containing a compound or compounds which include the approved product, imatinib mesylate. Claim 22 claims a method of treating tumors in warm-blooded animals with a compound or compounds which include the approved product, imatinib mesylate.

Claim 1 reads as follows:

1. An N-phenyl-2-pyrimidine-amine compound of formula I

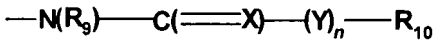


(I)

wherein

R_1 is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, amino- or amino-lower alkyl-substituted phenyl wherein the amino group in each case is free, alkylated or acylated, 1H-indolyl or 1H-imidazolyl bonded at a five-membered ring carbon atom, or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen,

R_2 and R_3 are each independently of the other hydrogen or lower alkyl, one or two of the radicals R_4, R_5, R_6, R_7 and R_8 are each nitro, fluoro-substituted lower alkoxy or a radical of formula II



(II)

wherein

R_9 is hydrogen or lower alkyl,

X is oxo, thio, imino, N-lower alkyl-imino, hydroximino or O-lower alkyl-hydroximino,

Y is oxygen or the group NH,

n is 0 or 1 and

R_{10} is an aliphatic radical having at least 5 carbon atoms, or an aromatic, aromatic-aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, heterocyclic or hetero-cycli-aliphatic radical,

and the remaining radicals R_4, R_5, R_6, R_7 and R_8 are each independently of the others hydrogen, lower alkyl that is unsubstituted or substituted by free or alkylated amino, piperazinyl, piperidinyl, pyrrolidinyl or by morpholinyl, or lower alkanoyl, trifluoromethyl, free, etherified or esterified hydroxy, free, alkylated or acylated amino or free or esterified carboxyl,

or a salt of such a compound having at least one salt-forming group.

When R_1 is unsubstituted pyridyl, R_2, R_3, R_5, R_6 and R_8 are hydrogen, R_4 is methyl, and R_7 is a radical of formula II where R_9 is hydrogen, X is oxo, n is 0 and R_{10} is an aromatic radical, and the compound is in methanesulfonate salt form, Claim 1 reads on the approved product, imatinib mesylate.

(10) Statement of Relevant Dates

The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) The patent for which the extension of the term is requested claims a human drug product. The human drug product is imatinib mesylate.

(b) An Investigational New Drug Application for imatinib mesylate was received by the Department of Health and Human Services on April 9, 1998 and the IND number assigned was 55,666.

(c) The New Drug Application was received by the Department of Health and Human Services on February 27, 2001 and the NDA number assigned was 21-335.

(d) NDA 21-335 was approved on May 10, 2001.

(11) Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix E is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in IND 55,666 and NDA 21-335.

(12) **Opinion of Eligibility for Extension**

Applicant is of the opinion that U.S. Patent No. 5,521,184 is eligible for extension under 35 U.S.C. §156 and 37 C.F.R. §1.720 because it satisfies all of the requirements for such extension as follows:

(a) **35 USC §156(a) and 37 CFR §1.720(a)**

U.S. Patent No. 5,521,184 claims imatinib mesylate, the active ingredient of a human drug product, pharmaceutical compositions thereof, and a method-of-use thereof.

(b) **35 USC §156(a)(1) and 37 CFR §1.720(g)**

The term of U.S. Patent No. 5,521,184 (expiring May 28, 2013) has not expired before the submission of this application.

(c) **35 USC §156(a)(2) and 37 CFR §1.720(b)**

The term of U.S. Patent No. 5,521,184 has never been extended.

(d) **35 USC §156(a)(3) and 37 CFR §1.720(c)**

The Application for extension of the term of U.S. Patent No. 5,521,184 is submitted by the authorized agent of the owner of record thereof in accordance with the requirements of 35 USC §156(d) and 37 CFR §1.740.

(e) **35 USC §156(a)(4) and 37 CFR §1.720(d)**

The approved product, GLEEVEC™, has been subjected to a regulatory review period before its commercial marketing or use.

(f) **35 USC §156(a)(5)(A) and 37 CFR §1.720(h)**

No other patent has been extended for the same regulatory review period for the approved product, GLEEVEC™.

(13) Length of Extension Claimed Under 37 CFR §1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 5,521,184 requested by Applicant is 599 days, which length was calculated in accordance with 37 CFR §1.775 as follows:

(a) The regulatory review period under 35 USC §156(g)(1)(B) began on April 9, 1998 (the filing date of the IND) and ended on May 9, 2001, amounting to a total of 1,126 days, which is the sum of (i) and (ii) below:

(i) The period of review under 35 USC §156(g)(1)(B)(i), the "Testing Period," began on April 9, 1998 and ended on February 26, 2001, which is 1,054 days;

(ii) The period for review under 35 USC §156(g)(1)(B)(ii), the "Application Period," began on February 27, 2001 and ended on May 9, 2001, which is 72 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (13)(a) above (1,126 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (December 17, 1985), i.e. zero days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e. zero days, and

(iii) One half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one half of (1,054 - [0+0]) or 527 days;

which results in a period of 1,126 - [0+0+527] = 599 days.

(c) The number of days as determined in subparagraph (13)(b), when added to the original term, would result in the date of January 17, 2015.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (May 10, 2001) would result in the date of May 10, 2015.

(e) The earlier date as determined by subparagraphs (13)(c) and (13)(d) is January 17, 2015.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 5,521,184 (May 29, 2013), results in the date May 29, 2018.

(g) The earlier date as determined in subparagraphs (13)(e) and (13)(f) is January 17, 2015.

(14) Duty of Disclosure Acknowledgment Under 37 CFR §1.740(a)(13)

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(15) Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

(16) Correspondence Address Required by 37 CFR §1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

Thomas Hoxie
Novartis Pharmaceuticals Corp.
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027

(17) Certification Under 37 CFR §1.740(a)(16)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 CFR §1.740(b).

Respectfully submitted,

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6921

Joseph J. Borovian
Agent for Applicant
Reg. No. 26,631

Date: July 3, 2001

APPENDIX A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APRIL 22, 1996

PTAS

CIBA-GEIGY CORPORATION
MICHAEL W. GLYNN
PATENT DEPARTMENT
520 WHITE PLAINS RD., P.O. BOX 2005
TARRYTOWN, NY 10591-9005

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/02/1996
REEL/FRAME: 7767/0596
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ZIMMERMANN, JURG
DOC DATE: 04/08/1994

ASSIGNEE:
CIBA-GEIGY CORPORATION
520 WHITE PLAINS ROAD, PATENT DEPARTMENT, P.O. BOX 2005
TARRYTOWN, NEW YORK 10591-9005

SERIAL NUMBER: 08234889
FILING DATE: 04/28/1994
PATENT NUMBER: 5521184
ISSUE DATE: 05/28/1996

JACQUELINE MOORE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

Copy Sent to Basle
4/29/96 Cmc

FORM PTO-1595 (Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET 01-30-1996

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Tab settings ⇨ ▼ ▼ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached documents or copy thereof. 100122241

1-2-96

1. Name of conveying party(ies):

JURG ZIMMERMANN

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: Michael W. Glynn

Internal Address: Ciba-Geigy Corporation
Patent Department

Street Address: 520 White Plains Road
P.O. Box 2005

City: Tarrytown State: NY ZIP: 10591-900

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: April 8, 1994

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)
08/234,889

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Michael W. Glynn

Internal Address: Ciba-Geigy Corporation
Patent Department

Street Address: 520 White Plains Rd.
P.O. Box 2005

City: Tarrytown State: NY ZIP: 10591-9005

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
07-0590

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

WT10089 01/19/96 08234889 07-0590 040 581 40.00CH

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Marla J. Mathias, 32,663 Marla J. Mathias 12-29-95

Name of Person Signing *certificate of mailing on reverse Signature Date

Total number of pages including cover sheet, attachments, and document: 2

US Case 4-19046/A/1968 CIP

ASSIGNMENT

I ~~(XXX)~~ Jürg Zimmermann of 4323 Wallbach, Switzerland

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to CIBA-GEIGY Corporation, a New York corporation, of 444 Saw Mill River Road, Ardsley, New York, 10502, U.S.A.,its successors, assigns and legal representatives, all my ~~(XXXX)~~ right, title and interest, in and for the United States of America, in and to the

Pryrimidine derivatives and processes for the preparation thereof

invented by me ~~(XXX)~~ and described in the application for United States Letters Patent therefor, executed on even date herewith, and all United States Letters Patent which may be granted therefor, and all divisions, reissues, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by the said CIBA-GEIGY Corporation, its successors, assigns or other legal representatives, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by me ~~(XXX)~~ if this assignment and sale had not been made;

And I ~~(XXXX)~~ hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to the said CIBA-GEIGY Corporation.

Signed on April 8, 1994

Jürg Zimmermann

FORM PTO-1595 (Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

PATENTS ONLY Case 4-19046/A/19689/CIP

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Ciba-Geigy Corporation

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: Novartis Corporation

Internal Address:

Street Address: 608 5th Avenue

City: New York State: N.Y. ZIP: 10020

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger

☐ Security Agreement ☒ Change of Name

☐ Other

Execution Date: December 31, 1996

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

B. Patent No.(s)
5,521,184

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Thomas Hoxie

Internal Address: Novartis Corporation

Patent and Trademark Dept.

Street Address: 564 Morris Avenue

City: Summit State: NJ ZIP: 07901-1027

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-0134 (in the name of Novartis Corporation)

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Joseph J. Borovian
Name of Person Signing
Reg. No. 26,631

Joseph J. Borovian
Signature

July 3 2001
Date

☒ Certificate of mailing on reverse side (Express Mail)

Total number of pages including cover sheet, attachments, and document: 2

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

CASE 4-19046/A/19689/CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT 5,521,184

ISSUED: May 28, 1996

INVENTOR: JÜRG ZIMMERMAN

FOR: PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF CHANGE OF NAME

Sir:

Attached hereto is a true and accurate copy of a certification by the Department of State of the State of New York, dated June 12, 1997, certifying, inter alia, the name change of Ciba-Geigy Corporation to Novartis Corporation, filed on December 31, 1996.

I, Thomas Hoxie, hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. Further, I am aware that willful and false statements and the like are punishable by fine or imprisonment, or both (18 USC§1001) and may jeopardize the validity of this document and any registration resulting therefrom.

Date: June 30, 2001

Thomas Hoxie
Vice President, Novartis Corporation
Reg. No. 32,993

State of New York
Department of State

SS:

I hereby certify, that the certificate of incorporation of NOVARTIS CORPORATION was filed on 11/15/1966, under the name of ARDSLEY CHEMICAL CORPORATION, with perpetual duration, and that a diligent examination has been made of the index of corporation papers filed in this Department for a certificate, order, or record of a dissolution, and upon such examination, no such certificate, order or record has been found, and that so far as indicated by the records of this Department, such corporation is a subsisting corporation. I further certify the following:

A Certificate of Merger and Name Change of ARDSLEY CHEMICAL CORPORATION, changing name to GEIGY CHEMICAL CORPORATION was filed on 12/30/1966.

A Certificate of Merger and Name Change of GEIGY CHEMICAL CORPORATION, changing name to CIBA-GEIGY CORPORATION was filed on 10/21/1970.

A Certificate of Amendment was filed on 12/19/1972.

A Certificate of Merger was filed on 12/29/1972.

A Certificate of Merger was filed on 12/19/1974.

A Certificate of Merger was filed on 12/24/1974.

A Certificate of Merger was filed on 12/26/1974.

A Certificate of Amendment was filed on 01/22/1979.

A Certificate of Amendment was filed on 08/24/1979.

A Certificate of Merger was filed on 12/26/1979.

A Certificate of Merger was filed on 12/26/1979.

A Certificate of Merger was filed on 11/02/1981.

A Certificate of Merger was filed on 12/17/1981.

A Certificate of Merger was filed on 12/29/1983.

A Certificate of Merger was filed on 12/19/1984.

A Certificate of Merger was filed on 03/31/1987.

A Certificate of Merger was filed on 06/26/1987.

A Certificate of Merger was filed on 01/26/1988.

A Certificate of Merger was filed on 12/30/1988.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 12/23/1991.

A Certificate of Merger was filed on 05/22/1992.

A Biennial Statement was filed 12/10/1992.

A Certificate of Merger was filed on 12/22/1992.

A Biennial Statement was filed 12/09/1993.

Certificate of change was filed on 06/02/1995.

A Certificate of Merger and Name Change of CIBA-GEIGY CORPORATION, changing name to NOVARTIS CORPORATION was filed on 12/31/1996.

Certificate of change was filed on 04/14/1997.

The Corporation Biennial Statement is past due.

I further certify, that no other certificates have been filed by such corporation.

Witness my hand and the official seal of the Department of State at the City of Albany, this 12th day of June one thousand nine hundred and ninety-seven.

Special Deputy Secretary of State

199706130195 37

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,521,184

ISSUED: MAY 28, 1996

INVENTOR: JÜRG ZIMMERMAN

FOR: PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY

Sir:

Novartis Corporation, a New York Corporation having offices at 608 Fifth Avenue, New York, New York 10020, being the owner of the entire title and interest in and to U.S. Patent No. 5,521,184, which was granted on May 28, 1996 to Jürg Zimmerman and entitled "PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF", hereby appoints the attorneys and agents associated with customer No. 001095, respectively and individually, each of them with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

Please direct all telephone calls to Joseph J. Borovian at (908) 522-6921, and all correspondence to Thomas Hoxie at Novartis Pharmaceuticals Corporation, Patent and Trademark Department, 564 Morris Avenue, Summit, New Jersey 07901-1027.

Thomas Hoxie
Vice President, Novartis Corporation
Reg. No. 32,993

June 30, 2001

APPENDIX C

US005521184A

United States Patent [19]

Zimmermann

[11] Patent Number: 5,521,184

[45] Date of Patent: May 28, 1996

[54] **PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF**

[75] Inventor: **Jürg Zimmermann**, Wallbach, Switzerland

[73] Assignee: **Ciba-Geigy Corporation**, Tarrytown, N.Y.

[21] Appl. No.: **234,889**

[22] Filed: **Apr. 28, 1994**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 42,322, Apr. 2, 1993, abandoned.

[30] **Foreign Application Priority Data**

Apr. 3, 1992 [CH] Switzerland 1083/92
Oct. 1, 1993 [CH] Switzerland 2966/93

[51] **Int. Cl.**[6] **C07D 239/92**; A61K 31/505

[52] **U.S. Cl.** **514/252**; 514/272; 544/295; 544/322; 544/331; 544/332

[58] **Field of Search** 514/252, 272; 544/295, 322, 331, 332

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,694,009	9/1987	Hubele et al.	514/269
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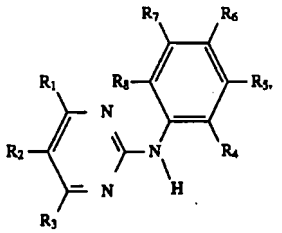
89-167195 Derwent Abstract (1989) corresponding to EP 319,170—Pfizer Inc.

Primary Examiner—Mukund J. Shah
Assistant Examiner—Matthew V. Grumbling
Attorney, Agent, or Firm—Karen G. Kaiser

[57] **ABSTRACT**

There are described N-phenyl-2-pyrimidine-amine derivatives of formula I



(I)

wherein

R_1 is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, amino- or amino-lower alkyl-substituted phenyl wherein the amino group in each case is free, alkylated or acylated, 1H-indolyl or 1H-imidazolyl bonded at a five-membered ring carbon atom, or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen, R^2, R^3, R^9, X, Y, n and R^{10} are defined in claim 1.

These compounds can be used, for example, in the therapy of tumoral diseases.

23 Claims, No Drawings

APPENDIX D

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

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564 MORRIS AVENUE
SUMMIT NJ 07901-1027

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.
If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,521,184	183	940	----	08/234,889	05/28/96	04/28/94	04	NO	PAI

ITM NBR	ATTY DKT NUMBER
1	419046A19689

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

APPENDIX E

Chronology of significant regulatory activities between Applicant and FDA during the IND and NDA periods:

IND PERIOD

4/9/98	Submitted IND application, which was assigned IND No. 55,666, together with Protocol 03 001, entitled: "A phase I, dose-finding study...resistant to interferon-alpha."
5/8/98	Received FAX from FDA referring to the Original IND and listing deficiencies from the reviewing chemist and medical officer which need to be addressed before the start of the clinical study.
5/13/98	Sent FAX to FDA in response to the deficiencies listed in the May 8, 1998 facsimile regarding Protocol No. 03 001.
5/27/98	Received FAX from FDA containing suggestions from the medical officer concerning revising the dose escalation scheme.
5/28/98	Sent FAX to FDA accepting the revised dose escalation scheme proposed by the FDA Medical Officer in the fax dated May 27, 1998.
6/23/98	Submitted FDA chemistry review comments and Novartis' response.
6/23/98	Submitted Amendment No. 1 to Protocol No. 03 001.
7/22/98	Submitted the following new investigator to Protocol No. 03 002: Dr. Charles L. Sawyers.
8/20/98	Submitted the following new investigator to Protocol No. 03 001: Dr. Moshe Talpaz.

APPENDIX

Chronology of significant regulatory activities between Applicant and FDA during the IND and NDA periods:

IND PERIOD

4/9/98	Submitted IND application, which was assigned IND No. 55,666; together with Protocol 03 001, entitled: "A phase I, dose-finding study...resistant to interferon-alpha."
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5/13/98	Sent FAX to FDA in response to the deficiencies listed in the May 8, 1998 facsimile regarding Protocol No. 03 001.
5/27/98	Received FAX from FDA containing suggestions from the medical officer concerning revising the dose escalation scheme.
5/28/98	Sent FAX to FDA accepting the revised dose escalation scheme proposed by the FDA Medical Officer in the fax dated May 27, 1998.
6/23/98	Submitted FDA chemistry review comments and Novartis' response.
6/23/98	Submitted Amendment No. 1 to Protocol No. 03 001.
7/22/98	Submitted the following new investigator to Protocol No. 03 002: Dr. Charles L. Sawyers.
8/20/98	Submitted the following new investigator to Protocol No. 03 001: Dr. Moshe Talpaz.

1/21/99	Submitted Amendment Nos. 2 and 3 to Protocol No. 03 001.
3/9/99	Submitted elevated SGPT and elevated SGOT from Dr. Talpaz.
3/25/99	Submitted Amendment No. 4 to Protocol No. 03 001.
4/21/99	Requested a meeting with the Division to discuss the adequacy of Novartis' proposed program to support registration for treatment of patients with advanced leukemias. Also requested for Fast Track designation. Included was a description of the development plan for the above indication.
4/23/99	Received FAX from FDA which includes an outline of the information that should be included in briefing package for an EOP1/EOP2 meeting. Additionally, included was a proposed format for a CMC meeting.
5/14/99	Submitted Briefing Book for End-of-Phase I/II meeting scheduled for June 15, 1999 to discuss Novartis' development plan and registration program for STI 571, formerly CGP 57148B, for treatment of chronic myeloid leukemia and myeloid blast crisis.
5/19/99	Requested Subpart E and Fast Track designation for the IND.
5/25/99	Submitted Amendment No. 5 to Protocol No. 001.
6/4/99	Received FDA LETTER acknowledging receipt of Novartis' request for Fast Track designation dated May 19, 1999 for the IND.
6/8/99	In preparation of the June 15, 1999 meeting, provided a revision of Question 4 in the topics for discussion of the Briefing Book.

6/15/99	An FDA/Novartis meeting summary and FDA minutes detail this of the End-of-Phase I/II meeting concerning the proposed program to support the treatment of patients with chronic myeloid leukemia in myeloid blast crisis.
7/14/99	Received FDA LETTER granting our request for Fast Track designation.
7/15/99	Submitted new protocols: Study No. CST 1571 0102, entitled: "A phase II, open label study to determine the safety and antileukemic effects of STI 571 in patients with Philadelphia chromosome positive chronic myeloid leukemia..."; and Study No. CST 1571 0109, entitled: "A phase II study ...in adult patients with Philadelphia chromosome positive leukemia including...chronic myeloid leukemia."
7/16/99	Submitted request to the Medical Reviewer to comment on the faxed Amendment No. 6 which allows the inclusion of patients 18 years old or younger.
7/16/99	Sent FAX to FDA for a protocol extension for two patients which included a brief history of their disease, the proposed treatment plan and a draft Amendment No. 6.
7/19/99	Submitted Amendment No. 6 to Study No. 03 001.
7/19/99	Received FAX from FDA containing the proposed Amendment No. 6 to treat pediatric patients. FDA concurred with the request to treat the two patients on the amendment protocol.
7/23/99	Received FAX from FDA providing additional comments form the Clinical Pharmacology and Biopharmaceutics Reviewer regarding our registration program (Meeting of June 15, 1999).

8/2/99	Submitted Amendment No. 7 to Study No. 03 001.
8/23/99	Received FDA LETTER informing Novartis that Protocol No. CST 1571 010 submitted July 15, 1999 (Serial No. 012) for a special clinical protocol assessment is being reviewed.
8/23/99	Received FDA LETTER informing Novartis that Protocol No. CST 1571 0190 contained in the submission dated July 15, 1999 (Serial No. 012) does not qualify for special protocol assessment because the protocol does not fit within the criteria for special assessment.
8/23/99	Received FAX from FDA regarding special protocol assessment requests for two protocols which are currently under review.
8/26/99	Received FAX from FDA commenting on Protocol No. 0109 submitted July 15, 1999 (Serial No. 012).
8/26/99	Received FDA LETTER responding to our July 15, 1999 request (Serial No. 012) for a special clinical protocol assessment on CSTI 571 0102. Medical and statistical comments were provided.
8/26/99	Received FAX from FDA commenting on Protocol No. 03001 submitted May 25, 1999 (Serial No. 011).
9/9/99	Submitted new investigators for Study No. STI 571 0102: Drs. Brian Druker, Charles L. Sawyers and Moshe Talpaz and new investigator to Study No. STI 571 0109: Dr. Moshe Talpaz.
9/10/99	Received FDA LETTER requesting an Annual Report within 30 days.
9/10/99	Received FAX from FDA requesting statistical information on the July 15, 1999 submission of Serial No. 012.

9/10/99	Submitted Annual Report covering the period April 14, 1998 through April 13, 1999. Clinical information and CMC changes were included.
9/28/99	Submitted new investigator to Study No. STI 571 0109: Dr. Brian Druker.
10/12/99	Submitted Amendment No. 1 to Study No. CSTI 571 0102; submitted Amendment No. 1 to CSTI 571 0109.
10/29/99	Submitted a request for an expedited Type B (End-of-Phase I/II) meeting to discuss the development of STI 571 in patients with interferon-refractory/intolerant chronic myelogenous leukemia. The following information was included: purpose, objectives/outcome, proposed agenda, planned Novartis attendees, requested CDER representatives and availability of supporting documentation.
11/5/99	Submitted Briefing Book containing a draft protocol and specific proposals for consideration for the End-of-Phase II teleconference to discuss the clinical development plan and registration program for STI 571 in the treatment of patients with interferon-refractory/intolerant chronic myelogenous leukemia (CML).
11/8/99	Submitted Extension No. 1 to Protocol No. CST 1571 0109.
11/12/99	Submitted new investigators to Study No. STI 571A 109: Drs. Charles L. Sawyers, Charles Schiffer and Richard T. Silver.
11/15/99	Submitted findings of Dr. Hagop Kandarjian, of fever.
11/15/99	Received FAX from FDA containing a request from the Medical Reviewer for Protocol No. 0110 references submitted in the November 5, 1999 briefing package.

11/17/99	In response to FDA facsimiles of November 15 and 16, 1999, submitted the additional information requested for the End-of-Phase I/II meeting/teleconference scheduled for December 7, 1999.
11/18/99	Submitted an update of preliminary results in the ongoing Phase I study to provide additional background for the End-of Phase I/II meeting/teleconference scheduled for December 7, 1999.
12/6/99	Submitted FAX to FDA containing information in preparation for the December 7, 1999 teleconference.
12/7/99	Received FAX from FDA containing meeting minutes of the December 7, 1999 teleconference.
12/8/99	Submitted new investigators for Study No. STI 571 0102: Drs. Charles Schiffer and Richard T. Silver.
12/8/99	Submitted new protocol and draft Amendment No. 1 to Study No. CST 1571 0110, entitled: "A Phase II Study to Determine the Efficacy and Safety of STI 571 in Patients with Chronic Myeloid Leukemia...Refractory to or Intolerant of Interferon-Alpha."
12/10/99	Submitted Amendment No. 8 to Study No. 03 001.
12/10/99	Submitted CMC amendment updating the drug substance and drug product sections of the IND.
12/20/99	Received FAX from FDA containing review comments from the Clinical Pharmacology and Biopharmaceutics Reviewer on Serial No. 000.
12/21/99	Received FAX from FDA containing comments on Amendment No. 8 to Protocol No. 03 001, Serial No. 029, submitted on December 10, 1999.

12/22/99	Submitted Amendment No. 1 to Study No. CSTI 571 0110; Amendment No. 2 to Study No. CST 1571 0102; and Amendment No. 2 to CST 1571 0109.
12/23/99	Sent FAX to FDA in response to December 21, 1999 facsimile concerning Amendment No. 8 to Protocol No. 03 001.
1/20/2000	Submitted new investigators for Study No. 0110: Drs. Brian Druker, Charles L. Sawyers, Moshe Talpaz, and Richard Stone.
1/21/2000	Submitted a Proposed Pediatric Study Request for FDA's review and comment on a Phase I dose escalation and pharmacokinetic study to support the issuance of a Written Request for Pediatric Exclusivity. A new protocol, Study No. P9973, entitled: "A Phase I Study of STI 571 in Ph+ Leukemia..." was also included.
1/26/2000	Sent FAX to FDA regarding a 7-day IND Safety Report from Dr. Charles Schiffer concerning bleeding, hepatotoxicity and fever.
1/28/2000	Submitted additional findings from Dr. Charles Schiffer concerning bleeding, hepatotoxicity and fever.
2/2/2000	Received FAX from FDA requesting specific information on each pivotal or critical study to be discussed at the End-of-Phase I/II meeting. This information is to be submitted on a 3.5" diskette in Word 97 in the specified format provided.

2/2/2000	Submitted a request for an End-of-Phase I/II meeting to discuss the overall development/registration strategy for patients with chronic myelogenous leukemia. The following information was included: purpose/objective, proposed agenda, planned Novartis attendees, requested CDER representatives, and the availability of supporting (background) documentation.
2/9/2000	Received FAX from FDA containing comments and questions from the statistical review of the submission dated December 8, 1999, Serial No. 028 - new protocol and draft Amendment 1 to Study No. CST 1571 0110.
2/10/2000	Submitted Briefing Book for the End-of-Phase I/II meeting scheduled for March 10, 2000, containing an overview of the clinical development and registration programs, detailed protocol outlines, and specific proposals for consideration. A list of proposed Novartis attendees was included.
2/11/2000	In reference to a December 21, 1999 facsimile from the FDA, this correspondence provided the requested pre-clinical assessment of the potential for thrombotic events which does not alter Novartis' conclusion that the events were not related to STI 571.
2/16/2000	Submitted findings of Dr. Charles Schiffer: bleeding, liver failure, hepatotoxicity, encephalopathy and fever. (Follow-up report #1.5)
2/21/2000	Submitted new investigators to Study No. STI 571 0102: Drs. Richard Stone and Carole B. Miller; new investigator to Study No. STI 109 0109: Dr. Richard Stone; and new investigators for Study No. STI 571 0110: Drs. Charles Schiffer, Richard T. Silver, Carole B. Miller, Thomas Loughran and Martin S. Tallman.

2/23/2000	Submitted a point-by-point response to the July 23, December 2 and December 20, 1999 facsimiles providing comments and considerations from the Office of Clinical Pharmacology and Biopharmaceutics pertaining to the registration program for STI 571.
3/2/2000	Submitted addendum to the Briefing Book, submitted February 10, 2000, Serial No. 035, containing relevant sections from draft Protocol No. 0106 (randomized trail of STI 571 vs. interferon) in order for FDA to assess the acceptability of this trial as a confirmatory study for CML program.
3/7/2000	Submitted findings of cystitis hemorrhagic.
3/7/2000	Submitted findings of erythematous generalized exfoliative rash, and spongiatic mixed dermatitis with marked eosinophilia. (Follow-up report #1.2)
3/9/2000	Sent FAX to FDA on the findings of Dr. A Gratwohl (Switzerland): heart failure and renal failure. (Follow-up report #1.2)
3/14/2000	Received FDA FAX outlining the specifics of the May 3, 2000 meeting to discuss STI 571 and requesting Briefing Book by April 14, 2000.
3/16/2000	Faxed 7-day Safety Report to FDA (full 15-day report to follow).
3/16/2000	Submitted findings of Dr. A. Gratwohl on STI 157: heart failure and renal failure. (Follow-up report #2.3)

3/16/2000	Submitted Study No. P9973, Amendment #1, which added the risk of hepatotoxicity to the toxicity monograph and added instructions on how to administer STI 571 to patients who are unable to swallow the capsules; also medications that are known to significantly affect gastric pH are no longer prohibited.
3/16/2000	Submitted findings of profound aplasia of bone marrow, and fever.
3/16/2000	Submitted findings of Dr. Brian Druker: erthematous generalized exfoliative rash, and spongiatic mixed dermatitis with marked eosinophilia. (Follow-up report #1.2)
3/22/2000	Submitted findings of Dr. Richard T. Silver: incorrect date on initial (0.1) report; low platelet count, epistaxis, fever and chills. (Initial and follow-up reports #1.2)
3/24/2000	Submitted findings of Dr. Brian Druker: erythematous generalized exfoliative rash, and spongiatic mixed dermatitis with marked eosinophilia. (Follow-up report #2.3)
3/24/2000	Submitted findings of Dr. Oliver G. Ottmann (Germany): hemorrhagic pleural effusion and generalized bleeding.
3/27/2000	Submitted new protocols: Study No. CSTI 571 0113, entitled: "A study to determine the safety and efficacy of STI 571 in patients with chronic myeloid leukemia...resistant or refractory to interferon-alpha and intolerant of interferon-alpha" and Study No. CSTI 571 0114, entitled: "A study ...in patients with chronic myeloid leukemia in accelerated phase."
3/27/2000	Submitted Fax/telephone report of the findings of Dr. A. Gratwohl (Switzerland) on thrombocytopenia.
3/29/2000	Submitted the findings of Dr. Moshe Talpaz on anemia.

3/30/2000	Submitted new investigators to Study No. P9973: Drs. Paul Gaynon, John Holcenberg and Joseph P. Neglia.
3/31/2000	Submitted findings of Dr. Carlo Gambacorti (Italy) on dyspnea.
3/31/2000	Submitted findings of cystitis hemorrhagic. (Follow-up report #1.2)
4/4/2000	Submitted findings of Dr. A. Gratwohl (Switzerland) on thrombocytopenia. (Follow-up report #1.2)
4/5/2000	Submitted findings of Dr. Carlo Gambacorti (Italy) on dyspnea. (Follow-up report #1.2)
4/7/2000	Submitted findings of Prof. J.M. Goldman (Great Britain) on generalized edema.
4/12/2000	Authorized the FDA to reference this IND for a Private IND file by the National Cancer Institute.
4/13/2000	Submitted findings of Dr. Brian Druker on duodenal ulcer and gastrointestinal bleeding. (Follow-up report #1.2)
4/13/2000	Requested pre-clearance of proposed tradename Evolex (primary) or Evizen (back-up). Also included background information on our product to support the review.
4/13/2000	Authorized the FDA to reference this IND for a Private IND file by George D. Demetri, M.D., Medical Director, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute and Harvard Medical School.
4/14/2000	Submitted additional proposals for discussion at the upcoming End-of-Phase I/II meeting scheduled for May 3, 2000.

4/17/2000	Submitted findings of Dr. Richard T. Silver: low platelet count, epistaxis, fever and chills. (Follow-up report #2.3)
4/17/2000	Submitted additional findings of Dr. Richard T. Silver: profound aplasiam of bone marrow and fever. (Follow-up report #1.2)
4/18/2000	FDA submitted a package to National Cancer Institute containing a Certificate of Analysis and sample drug labels for STI 571.
4/18/2000	Submitted new protocol, Study No. CSTI 571 0106, entitled: "A phase III study of STI 571 versus Interferon-alpha (IFN-alpha)...in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase..." Also enclosed was an Addendum to Edition 2 of the Investigator's Brochure dated May 7, 1999. (NOTE: The alpha symbol is used in the protocol title).
4/19/2000	Submitted findings of Dr. A. Gratwohl: heart failure and renal failure. (Follow-up report #3.5)
4/21/2000	Submitted findings of Dr. Oliver G. Ottmann: hemorrhagic pleural effusion, deterioration of basic disease and generalized bleeding. (Follow-up report #1.2)
4/25/2000	Sent FAX to FDA regarding a 7-day IND Safety Report concerning Dr. Carole B. Miller's findings of CNS hemorrhage.
4/26/2000	Sent FAX to FDA containing a list of Novartis attendees for the May 3, 2000 meeting.
4/27/2000	Submitted findings of Dr. Carole B. Miller: gross hematuria, urinary retention, CNS hemorrhage and drug interaction/warfarin.

4/28/2000	Submitted findings of Prof. J.M. Goldman: generalized edema. (Follow-up report #1.2)
5/2/2000	Received FAX from FDA containing the Division's internal bullets and overheads for the May 3, 2000 End-of-Phase I/II meeting.
5/3/2000	Received FDA meeting minutes for the End-of-Phase I/II meeting held on May 3, 2000. Also included is a copy of the Division's bullets and overheads.
5/3/2000	Submitted findings of Dr. Carlo Gambacorti concerning dyspnea. (Follow-up report #2.4)
5/11/2000	Submitted new investigators to Study No. P9973/01013: Drs. W. Paul Bowman and Paulette Mehta; new investigators to Study No. ST 571 0102: Drs. Thomas Shea and Alan Saven; and a new investigator to Study No. STI 571 0110: Dr. Randy A. Brown.
5/11/2000	Submitted findings of Dr. Carole B. Miller: gross hematuria, urinary retention, CNS hemorrhage and drug interaction. (Follow-up report)
5/19/2000	Submitted findings of Dr. Carlo Gambacorti (Italy): fluid retention, dyspnea and weight gain.
5/24/2000	Submitted Amendment No. 9 to Study No. 03 001.
6/1/2000	Submitted Novartis' minutes of the May 3, 2000 End-of-Phase I/II meeting to discuss the registration program of STI 571 in the treatment of patients with chronic myelogenous leukemia.
6/1/2000	Submitted new investigators to Study No. STI 571 0102: Drs. M. Goodman, E. Berman, Steven E. Coutre and R. Larson; and a new investigator to Study No. P9973 0103: Dr. V. Shen.

6/14/2000	Sent FAX to FDA containing two versions (initial and follow-up report) of a 7-day IND Safety Report concerning the findings of Dr. Brian Druker: shock, gastrointestinal bleeding and increased creatinine.
6/15/2000	Submitted new protocol: Study No. CSTI 571 B2222, entitled: "Open, Randomized, phase II Study of STI 571 in Patients with Unresectable or Metastatic Malignant Gastrointestinal Stromal Tumors..." New investigator, Dr. Richard Pazdur.
6/20/2000	Submitted initial report/follow-ups of Dr. Brian Druker; #1: shock and gastrointestinal bleeding; #2: shock, creatinine increase and gastrointestinal bleeding; #3: pancytopenia, seborrheic dermatitis, pulmonary infection (possible ARDS), shock, creatinine increase, gastrointestinal bleeding and leukemia relapse; #4: pancytopenia, seborrheic dermatitis, pulmonary infection (possible ARDS), shock, creatinine increase, gastrointestinal bleeding and leukemia relapse; and #5: paroxysmal atrial fibrillation, pancytopenia, seborrheic dermatitis, chronic renal insufficiency and bilateral aspiration pneumonia.
6/21/2000	Submitted Annual Report covering the period from April 14, 1999 to April 13, 2000. Included pre-clinical and clinical study information, CMC changes and an addendum to Edition No. 2 of the Investigator's Brochure (dated May 7, 1999).
6/21/2000	Submitted new investigators to Study No. STI 571 0113: Drs. Carole B. Miller and Brian Druker; and a new investigator to Study No. STI 571 01143: Dr. Brian Druker.
6/22/2000	Sent E-mail to FDA regarding the supporting literature and amendment for Protocol No. 0106, submitted April 18, 2000, Serial No. 065, discussed at the May 3, 2000 meeting.

6/22/2000	Requested a pre-NDA meeting to discuss the CMC section of the application.
6/26/2000	Submitted Drug Substance and Drug Product update.
6/28/2000	In reference to the May 3, 2000 meeting, submitted an outline of the critical changes proposed to Study No. 0106 and included the rationale for the proposed crossover at six months for lack of complete hematologic response.
6/30/2000	Submitted findings of Dr. Charles L. Sawyers: bilateral lower extremity emboli.
7/11/2000	Sent FAX to FDA containing a draft amendment for Study No. 0106 in follow-up to the June 28, 2000 correspondence regarding Serial No. 084, providing an outline of revisions and the supporting documentation for the proposed study.
7/11/2000	Received FAX from FDA containing comments from the Clinical Pharmacology and Biopharmaceutics teams regarding Serial Nos. 029 and 039, dated December 10, 1999, and February 23, 2000, respectively.
7/18/2000	Received FDA LETTER providing concerns about the design of the Phase III chronic CML trial and requesting a final protocol as soon as possible.
7/20/2000	Submitted a Briefing Book for the August 18, 2000 CMC pre-NDA meeting with FDA. A list of Novartis attendees was also included.
7/20/2000	Submitted new protocol: Study No. CSTI 571 0115, entitled: "An open-labeled study to determine the efficacy and safety of STI 571 in patients with chronic myeloid leukemia in blast crisis."

7/25/2000	Submitted Amendment No. 1 and new investigator, Dr. Moshe Talpaz, to Study No. CST 571 0106. A meeting was also requested to discuss and resolve outstanding issues prior to finalization of the subsequent protocol amendment.
7/26/2000	Submitted a revised proposal for a back-up tradename to Glivec based on a rejection of the originally proposed (April 13, 2000) back-up tradename, Evizen, by the European Agency for evaluation of Medicinal Products (EMEA).
7/26/2000	Submitted findings of Dr. Carlo Gambacorti (Italy): amylase increase (suspected pancreatitis). (Initial report (0.1) and follow-up reports #1.2 and #2.3)
7/26/2000	Requested a pre-NDA meeting to discuss Novartis' approach for submitting the marketing application. The purpose, proposed agenda, planned Novartis attendees, requested CDER representatives, and availability of supporting documentation was also provided.
7/28/2000	Submitted new investigators to Study No. P9973 0103: Drs. S.A. Feig, S. Jeha and J. Pullen; Study No. CSTI 571 0106: Dr. J. Gabrilove; Study No. STI 571 0113: Drs. R.A. Brown, Steven E. Coutre and Moshe Talpaz; Study No. STI 571 0114: Drs. Steven E. Coutre and Moshe Talpaz; and Study No. STI 571 B2222: Dr. G.D. Demetri.
8/1/2000	Submitted findings of Dr. Moshe Talpaz: pancytopenia, paroxysmal atrial tachycardia and febrile neutropenia. (Initial and follow-up reports #1 and #2)
8/7/2000	Submitted new protocol: Study No. CSTI 571 0202, entitled: "Open label, multicenter, two-arm, two-stage phase II study of STI 571 in patients with extensive stage small cell lung cancer."

8/7/2000	Received FAX from FDA containing comments from the Clinical Pharmacology and Biopharmaceutics review of the submission dated May 24, 2000, Serial No. 075 - Amendment No. 9 to Study No. 03 001.
8/9/2000	Submitted findings of Prof. Josy Reiffers: hemodynamic shock and melena. (Initial and follow-up reports)
8/15/2000	In reference to the upcoming meeting, scheduled for August 31, 2000, to discuss study design elements of Protocol No. 0106 (phase III study), submitted an outline of the outstanding issues that remain to be resolved. Attachments included July 18, 2000 FDA LETTER, June 28, 2000 submission of Serial No. 084, Protocol No. 0106, Study Management Committee Operational Procedures and references.
8/15/2000	Received FAX from FDA containing the meeting specifics and attendees per meeting request dated July 25, 2000 (Serial No. 088).
8/17/2000	Received FAX from FDA containing answers to CMC questions in the briefing package for the pre-NDA meeting scheduled for August 18, 2000. (Serial No. 086, July 20, 2000)
8/23/2000	Submitted Briefing Book in preparation for the pre-NDA meeting, scheduled for September 21, 2000, to discuss the content and format of the NDA. The proposed Novartis attendees were included.
8/24/2000	Informed FDA that Serial No. 096 was inadvertently skipped, and since it would be unduly complex to correct the serial numbering, an agreement was reached between Novartis and FDA to send a note on the IND documenting the matter.

9/5/2000	Submitted new investigators to Study No. P9973 0103: Drs. B.M. Camitta and C.S. Kretschmar; Study No. SCTI 571 0106: Drs. S. Frankel, J. Gabrilove, J.P. Kuebler, R. Larson, J.L. Wade, Brian Drucker and R.K. Shadduck; Study No. STI 571 0113: Drs. T. Loughran and R.A. Brown; Study No. STI 571 0114: Drs. R. Larson, Carole B. Miller and C. Schniffer; and Study No. STI 571 2222; Drs. M.V. Mehren and C. Blanke.
9/7/2000	Submitted Amendment No. 2 to Study No. P9973 0103.
9/8/2000	Submitted response to facsimiles dated July 11 and August 7, 2000, which contained comments from the Clinical Pharmacology and Biopharmaceutics review.
9/12/2000	Received FDA LETTER in response to the Proposed Pediatric Study Request submitted on January 21, 2000. FDA made a formal Written Request that Novartis submit information (i.e., indications to be studied, study endpoints) from the various types of studies listed. The format and timeframe for submitting reports of the studies were also provided.
9/12/2000	Submitted Amendment No. 1 to Study No. CSTI 571 0202 and Amendment No. 1 to Study No. CSTI 571 B2222.
9/12/2000	Received FAX from FDA containing Clinical Pharmacology and Biopharmaceutics comments on Serial No. 32 - Proposed Pediatric Study Request. A copy of the Pediatric Written Request Letter was also included.
9/12/2000	Received FAX from FDA containing IND acknowledgment information, since an official acknowledgment letter was never received for this IND.

9/12/2000	Sent E-mail to FDA containing a word document with the proposed topics for discussion at the September 21, 2000 pre-NDA meeting.
9/12/2000	Received FAX from FDA containing the August 18, 2000 meeting minutes. It was noted that in reference to the Serial No. 086 submission dated July 7, 2000, comments on one of the issues will be provided prior to the September 21, 2000 pre-NDA meeting and will not be discussed at that time.
9/13/2000	Submitted new protocol: Study No. CSTI 571 0201, entitled: "An open-label, multicenter, phase II study to evaluate the ability of STI 571 to produce a sustained biochemical response in patients with a hormone-refractory prostate cancer."
9/15/2000	Submitted new investigators to Study No. CSTI 571 0106: Drs. M. Wetzler, R.L. Moroose, J.D. Bearden, H.M. Gross, P. Cobb, S.R. Dakhill, M. Dayton, J.O. Moore, B. Grant, B. Powell, L. Akard and R. Collins; Study No. STI 571 0113: Drs. Richard Stone, T. Shea, C. Schniffer and R.A. Larson; Study No. STI 571 0114: Drs. T. Shea and T. Loughran; and Study No. STI 571 0115: Drs. Steven E. Coutre and Brian Druker.
9/18/2000	Sent FAX to FDA containing a replacement page for the pre-NDA meeting book submitted on August 23, 2000 (Serial No. 098).
9/19/2000	Sent FAX to FDA containing a 7-day Safety Report regarding the findings of Dr. Ebnother (Basel), Protocol No. 990045: hydrocephalus NOS, nausea, vomiting NOS and headache NOS.
9/20/2000	Received FAX from FDA containing the August 31, 2000 meeting minutes.

9/20/2000	In reference to a request from the Biopharmaceutics reviewer, submitted a draft clinical pharmacology report (Study No. 109, Extension + 110 of Amendment 2), entitled: "A Phase II study to investigate the effects of food on the bioavailability of STI 571...in patients suffering from chronic myeloid leukemia (CML)."
9/21/2000	Received FAX from FDA containing comments regarding the D6 issue in reference to the August 18, 2000 pre-NDA meeting minutes and to the Briefing Book submitted on July 20, 2000 (Serial No. 086).
9/26/2000	Sent FAX to FDA containing a 7-day Safety Report regarding the findings of Dr. Charles L. Sawyers (Protocol No. 003 001): neutropenia and sepsis NOS.
9/28/2000	Submitted findings of Dr. Ebnother (Basel), Protocol No. 990045: hydrocephalus NOS, nausea, vomiting NOS and headache NOS.
9/29/2000	In reference to the pre-NDA CMC meeting with FDA on August 18, 2000, submitted FAX to FDA requesting feedback on the attached packaging and stability proposal.
10/2/2000	Submitted amendment which represents the official copy of a facsimile to FDA, dated September 29, 2000, which requested concurrence on a proposal for additional packaging configurations of STI 571 for inclusion in the upcoming NDA.
10/3/2000	Submitted findings of Dr. Moshe Talpaz (Protocol No. 0102): atrial tachycardia, febrile neutropenia and pancytopenia. (Follow-up report #1)
10/4/2000	Submitted a draft amendment to Protocol No. 0106 incorporating the changes as discussed in the August 31, 2000 meeting.

10/4/2000	Submitted the findings of Dr. Charles L. Sawyers (Protocol No. 003 001): neutropenia and sepsis NOS.
10/6/2000	In reference to the correspondence submitted on April 13 and July 26, 2000, requested pre-clearance of a proposed tradename (this submission provides a revised proposal for the tradename, Glivec) and a copy of the draft labeling.
10/10/2000	Submitted findings of Dr. Thierry Falcon (France), Protocol No. CSTI 571 0114: duodenal ulcer, duodenal perforation, pneumoperitoneum, hypotension NOS, duodenal ulcer hemorrhage and hematemesis.
10/13/2000	Submitted new investigators to Study No. 0106: Drs. T.M. Beck, Richard.T. Silver, S. Graziano, P. Emanuel, D.H. Irwin, Z.S. Pavletic, E. Layhe, G. Herzig, H.A. Burris, B.A. Peterson, D. Stirewait, L.A. Kalman, D.K. Strickland, Richard Stone and D.A. Stevens; Study No. 0113: Dr. Richard Stone; Study No. 0114: Dr. Richard T. Silver; and Study No. 0115: Dr. Moshe Talpaz.
10/13/2000	Submitted an amendment containing manufacturing and controls information to support the use of an intravenous (IV) formulation.
10/13/2000	Submitted findings of Prof. J.M. Goldman (Great Britain), Protocol No. CSTI 571 0102: sepsis NOS, neutropenia, pytexia, weakness, tachycardia NOS, hypotension NOS and rigors.
10/13/2000	Submitted findings of Dr. SSA Ester Orlandi (Italy), Protocol No. CSTI 571 A2214: deep limb venous thrombosis and lower limb edema.
10/18/2000	Sent E-mail to FDA stating it is unnecessary to proceed with review of the CMC amendment, Serial No. 115, dated October 13, 2000, to support IV formulation for a single patient.

10/18/2000	Received FDA FAX with suggestions from the Medical Officer after completing review of draft Protocol No. 0106, Serial No. 110, submitted on October 4, 2000.
10/20/2000	Sent FAX to FDA containing 7-day Safety Report regarding findings of Dr. Richard Stone (Protocol No. CSTI 571 0113) of myocardial infarction.
10/26/2000	Received FAX from FDA containing chemistry review comments and responses to the proposed additional packaging configurations submitted on October 2, 2000, Serial No. 108.
10/26/2000	Submitted findings of Dr. George Demetl (Protocol No. CSTI 571 B2222): small intestinal obstruction NOS, nausea, vomiting NOS, pyreia, anemia NOS and tumor hemorrhage.
10/26/2000	Submitted findings of Dr. SSA Ester Orlandi (Italy) (Protocol No. CSTI 571A 2214/CML/003/STI 571): deep limb venous thrombosis and lower limb edema. (Follow-up report #1)
10/26/2000	Submitted findings of Prof. J.M. Goldman (Great Britain), Protocol No. CSTI 571 0102: sepsis NOS, neutropenia, pyrexia, weakness, tachycardia NOS, hypotension NO and rigors. (Follow-up report #1)
10/31/2000	Submitted findings of Dr. Richard Stone, Protocol No. CSTI 571 0113: myocardial infarction.
10/31/2000	Submitted findings of Dr. SSA Enrica Morra (Italy), Protocol No. CSTI 571 0110: stress symptoms and dizziness (exc. vertigo).
11/3/2000	Sent FAX to FDA of a 7-day IND Safety Report containing findings of Dr. Steven E. Coutre (Protocol No. STI 571 0113): angioedema (angioneurotic edema).

11/3/2000	Submitted findings of Dr. Brian Druker (Protocol No. CSTI 571 0109): retinal edema (exc. papilloedema).
11/7/2000	In response to FDA comments dated October 18, 2000, submitted a revised protocol amendment for Study No. 0106 to incorporate the changes which were also consistent with the advice the Agency provided in the December 7, 1999 teleconference and the May 3 and August 31, 2000 meetings.
11/9/2000	Submitted new investigators to Study No. 0103: Drs. B. Lange, J.E. Rubnitz, T.M. Trippett and R.J. Wells; Study No. 0106: Drs. R.A. Brown, M. Lobell, L. Elias, P. Ely, M. Kalaycio, W. E. Samlowski, E. Berman, R.G. Smith, M. Shurafa, A. Bashey, S. Cooper, Martin S. Tallman and R. Veith; Study No. 0113: Drs. Martin S. Tallman and R. Paquette; Study No. 0114: Drs. Richard Stone, E. Berman, Martin S. Tallman and R.A. Brown; Study No. 0115: Drs. H. Saba, C. Schniffer, R.A. Brown and Richard T. Silver; and Study No. 0201: Dr. L.A. Kalman.
11/10/2000	Sent FAX to FDA containing a 7-day IND Safety Report regarding Dr. Richard Larson's findings (Protocol No. STI 571 0114): cardiac tamponade and pericardial effusion.
11/13/2000	In follow-up to FDA comments on the proposals in the August 23, 2000 pre-NDA Briefing Book (Serial No. 098), proposed a meeting to discuss the various options of a shared/joint review of the NDA among the FDA and the regulatory authorities of Canada (Health Canada's Therapeutic Products Program, TPP) and Japan (Ministry of Health & Welfare, MHW).
11/14/2000	Submitted findings of Dr. Steven E. Coutre (Protocol No. CSTI 571 0113): angioneurotic edema.

11/16/2000	Submitted findings of Dr. Richard Larson (Protocol No. STI 571 0114): cardiac tamponade and pericardial effusion.
11/22/2000	Submitted findings of Dr. Carole B. Miller (Protocol No. STI 571 0114) of folliculitis.
11/28/2000	TELECONFERENCE with FDA to discuss a shared/collaborative review of the STI 571 dossier with other health authorities in response to Novartis' November 13, 2000 correspondence.
12/1/2000	Submitted findings of Dr. Carlo Gambacorti (Protocol No. 0109): pancreatitis NOS.
12/1/2000	Submitted findings of Dr. Carole B. Miller (Protocol No. 0114): paresthesia NEC and pain in limb.
12/5/2000	Sent FAX to FDA containing a 7-day IND Safety Report (Protocol No. STI 571 0114): pericardial effusion, rash, liver injury during procedure, adult respiratory distress syndrome, multi-system organ failure and sepsis.
12/5/2000	Sent E-mail to FDA containing final draft versions of four ASH abstracts that present the preliminary data from the phase II studies #102, #109 and #110.
12/7/2000	Submitted new investigators to Study No. 0103: Dr. P.M. Rosoff; Study No. 0106: Drs. S. Cataland, D.G. Morrison, B. Issell, S.A. Limentani, P.S. Becker, Mark W. Brunvand, A.M. Keller, M.E. Agha, H. Holmes and C. Rosenfeld; and Study No. 0115: Drs. Richard Stone, R. Larson and T. Shea.
12/7/2000	Submitted Amendment No. 1 to Study No. CSTI 571 0114.

12/7/2000	Submitted findings of Dr. Steven E. Coutre (Protocol No. STI 571 0114): convulsions NOS.
12/7/2000	Submitted findings of Dr. A. Gratwohl (Switzerland), Protocol No. CSTI 571 0110: cholelithiasis.
12/8/2000	Submitted findings of Dr. Carole B. Miller (Protocol No. STI 571 0114): pericardial effusion, folliculitis, hepatic trauma, acute respiratory distress syndrome, multi-organ failure, sepsis NOS, hypovalemic shock, dyspnea NOS and disseminated intravascular coagulation.
12/11/2000	Submitted findings of Dr. Martino Cervellera (Italy) (Protocol No. CSTI 571 A2214): bronchopneumonia NOS, chest pain NEC, pleurisy, rigors and pyrexia.
12/12/2000	Received FDA LETTER responding to the November 7, 2000 request (Serial No. 124) for a special clinical protocol assessment. Responses to Novartis' questions and comments were also provided.
12/12/2000	Received FAX from FDA stating that the Medical Officer approved the special patent exception request as detailed in the December 12, 2000 correspondence (Serial No. 138).
12/12/2000	Advised the FDA of a special protocol exception to Study No. 0102 by Dr. Carole B. Miller, an investigator in this study. IRB approval has been obtained and informed consent will be obtained prior to reinitiating therapy.
12/15/2000	Submitted findings of Dr. Tanya Trippett (Protocol No. STI 571 0103): blood culture positive, neutrophil count decrease, pulmonary congestion, hypotension NOS, pulse pressure decrease and fatigue pyrexia.

12/15/2000	Submitted findings of Dr. Richard Stone (Protocol No. CSTI 571 0109): neutropenia, pneumonia NOS, dyspnea NOS and cough.
12/19/2000	Submitted findings of Dr. Lina Mangoni (Italy) (Protocol No. CSTI 571 A2213): syncope, pyrexia and tachycardia NOS.
12/19/2000	Sent FAX to FDA containing a 7-day Safety Report regarding findings of Dr. Steven E. Coutre (Protocol No. STI 571 0114): fungal sepsis (systemic fungal infection NOS), fever and neutropenia (febrile neutropenia); wet purpura and petechia (purpura NOS), gastrointestinal bleeding (gastrointestinal hemorrhage NOS), herpes simplex I pneumonia (pneumonia viral NOS) and pancytopenia.
12/20/2000	Submitted findings of Dr. Steven E. Coutre (Protocol No. STI 571 0114): systemic fungal infection NOS, febrile neutropenia, purpura NOS, gastrointestinal hemorrhage NOS, pneumonia viral NOS and pancytopenia.
12/20/2000	Submitted findings of Dr. Steven E. Coutre (Protocol No. STI 571 0114) of syncope.
12/21/2000	Submitted findings of Dr. Carole B. Miller (Protocol No. STI 571 0114): pericardial effusion, folliculitis, hepatic trauma, acute respiratory distress syndrome, multi-organ failure, sepsis NOS, hypovalemic shock, dyspnea NOS and disseminated intravascular coagulation.
12//21/2000	Submitted findings of Dr. Oliver G. Ottmann (Germany) (Protocol No. CSTI 571 0114): intracranial hemorrhage NOS, subdural hygroma, thrombocytopenia and headache NOS.
12/21/2000	Requested a Type B (End-of-Phase I/II) meeting to discuss the acceptability of the registration program for patients with

	unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). The availability of supporting documentation and the planned Novartis attendees and requested CDER representatives were also provided.
12/22/2000	Sent FAX to FDA containing two 7-day Safety Reports regarding the findings of: 1) Dr. Anna D'Emilio (Italy) (Protocol No. CSTI 571 A2214): cardiac failure NOS, chest pain NEC and myocardial ischemia; and 2) Dr. Carlos Sergio Chiattone (Brazil) (Protocol No. CSTI 571 0115): staphylococcal septicemia, pancytopenia and renal impairment NOS.
12/22/2000	Submitted findings of Dr. Steven E. Coutre (Study Protocol No. CSTI 571 0115): febrile neutropenia, staphylococcal infection NOS and enterococcal urinary tract infection.
12/22/2000	Submitted findings of Dr. Vaneuza Araugo Moreira (Brazil) (Study Protocol No. CSTI 571 0114): convulsions NOS.
12/29/2000	Submitted findings of Dr. Carlos Sergio Chiattone (Brazil) (Protocol No. CSTI 571 0115): staphylococcal septicemia, pancytopenia, renal impairment NOS, pneumonia NOS and respiratory failure (exc. neonatal).
12/29/2000	Submitted findings of Dr. Anna D'Emilio (Italy) (Protocol No. CSTI 571 A2214): cardiac failure NOS, chest pain NEC and myocardial ischemia.
12/29/2000	Submitted findings of investigator Dr. Martino Cervellera (Italy) (Protocol No. CSTI 571 A2214): bronchopneumonia NOS, chest pain NEC, pleurisy, rigors and pyrexia.
12/29/2000	Submitted findings of Dr. John Graham-Pak (Protocol No. STI 571 0103): aseptic bone necrosis.

1/3/2001	Submitted findings of Dr. Anna D'Emilio (Italy) (Protocol No. CSTI 571 A2214): cardiac failure NOS, chest pain NEC and myocardial ischemia.
1/9/2001	Sibmitted CMC amendment containing updated composition and manufacturing information for the drug product in support of an increase in the 100 mg. capsule batch size, along with the use of red ink for printing on the capsules.
1/12/2001	Submitted findings of Dr. Steven E. Coutre (Protocol No. CSTI 571 0115): sepsis NOS, pancytopenia, enterococcal urinary tract infection, pneumonia NOS, staphylococcal infection NOS and febrile neutropenia.
1/15/2001	Submitted a special protocol exception to Study No. 0114 for a patient under 18 years of age who will be treated by Dr. Carole B. Miller, a Principal Investigator in Study No. 0114. IRB approval and informed consent will be obtained from the parent.
1/16/2001	Received FAX from FDA approving special protocol exception submitted on January 15, 2001 (Serial No. 156).
1/18/2001	Submitted findings of Dr. Anna D'Emilio (Italy) (Protocol No. CSTI 571 A2214): cardiac failure NOS, chest pain NEC and myocardial ischemia.
1/18/2001	Submitted new investigators to Study No. 0106: Drs. R. Bhatia, P. Rintels, H.B. Neill, T.E. Seay, T. Shea, R. Hart and A. Pecora; Study No. 0115: Dr. Martin S. Tallman; Study No. 0102: Dr. S.A. Kuross; and Study No. 0202: Dr. B.E. Johnson.
1/19/2001	Submitted findings of Carole B. Miller (Protocol No. STI 571 0114): paresthesia NEC, pain in limb and disease progression NOS.

1/19/2001	Submitted findings of Dr. Carlos Sergio Chiattone (Brazil) (Protocol No. CSTI 571 0115): staphylococcal septicemia, pancytopenia, renal impairment NOS, pneumonia NOS and respiratory failure.
1/19/2001	Submitted findings of Dr. Tanya Trippett (Protocol No. STI 571 0103): candidal infection NOS.
1/22/2001	Submitted letter to FDA authorizing the exchange of information with the health authorities of Canada, Australia, and Japan throughout the review of the NDA. A list of contact information for each health authority was also submitted.
1/22/2001	Sent FAX to FDA containing a 7-day Safety Report regarding the findings of Dr. Hagop Kantarjian (Protocol No. STI 571 0114): pancytopenia (pacytopenia), sepsis NOS, pharyngitis NOS and abscess NOS.
1/24/2001	Submitted protocol amendments to each of the expanded access program (EAP) protocols: Nos. 0113, 0114 and 0115.
1/24/2001	Submitted findings of Dr. SSA Eliana Zuffa (Italy) (Protocol No. CSTI 571 A2214): aggravated psoriasis.
1/24/2001	Submitted findings of Dr. Vaneuza Araugo Moreira (Brazil) (Protocol No. CSTI 571 0114): aggravated malignant neoplasm and convulsions NOS. (Follow-up report)
1/26/2001	Sent FAX to FDA containing a 7-day Safety Report regarding findings of Prof. Straetmans (Belgium) (Protocol No. CSTI 571 0115): septic shock, aggraved malignant neoplasm, drug ineffectiveness, pyrexia, dyspnea NOS and hypotension NOS.

1/26/2001	Received FAX from FDA containing comments from the Clinical Pharmacology Reviewer on Serial No. 106 (Food Effect Study), submitted on September 20, 2000.
1/30/2001	Submitted findings of Dr. Carole B. Miller (Protocol No. STI 571 0114): pericardial effusion, folliculitis, hepatic trauma, acute respiratory distress syndrome, multi-organ failure, sepsis NOS, hypovalemic shock, dyspnea NOS and disseminated intravascular coagulation. (Follow-up report)
1/31/2001	Submitted findings of Dr. Hagop Kantarjian (Protocol No. STI 571 0114): pancytopenia, sepsis NOS, pharyngitis NOS and abscess NOS.
2/1/2001	Submitted findings of Prof. Straetmans (Belgium) (Protocol No. CSTI 571 0115): septic shock, aggravated malignant neoplasm, drug ineffectiveness, pyrexia, dyspnea NOS and hypotension NOS.
2/1/2001	Submitted findings of Dr. Steven E. Coutre (Protocol No. CSTI 571 0115): sepsis NOS, pancytopenia, enterococcal urinary tract infection, pneumonia NOS, disease progression NOS, drug ineffectiveness, staphylococcal infection NOS and febrile neutropenia. (Follow-up report)
2/2/2001	Sent letter authorizing the FDA to refer to this IND to support an IND to be filed by Dr. H.M. Kantarjian.
2/5/2001	Submitted new protocol, Study No. CSTI 571 B2225, entitled: "Open Label, Pilot II Study of STI 571 in Patients with Life Threatening Diseases...Associated with one or More STI 571-Sensitive Tyrosine Kinases."

2/6/2001	Submitted findings of Dr. Steven E. Coutre: (Protocol No. STI 571 0114): systemic fungal infection NOS, febrile neutropenia, purpura NOS, gastrointestinal hemorrhage NOS, pneumonia, viral NOS and pancytopenia. (Follow-up report)
2/6/2001	Submitted findings of Dr. Lina Mangoni (Italy) (Protocol No. CSTI 571 A2213): deep limb venous thrombosis and lower limb edema.
2/9/2001	Submitted new investigators to Study No. 0106: Drs. J. Kolitz, K.R. Rai, S. Devine, H. Safah, M.D. Rubenstein and B. Meisenberg.
2/14/2001	Received FAX from FDA containing comments and a request for information on Serial No. 101, dated September 7, 2000.
2/14/2001	Submitted findings of Dr. Carole B. Miller (Protocol No. CSTI 571 0113): pancreatitis NOS, nausea, vomiting NOS and upper abdominal pain.
2/15/2001	Sent letter authorizing the FDA to refer to this IND to support an IND to be filed by Dr. A. Raza.
2/15/2001	Received FAX from FDA containing comments from the Clinical Pharmacology Reviewer on Amendment No. 2 to Study No. 0103, Serial No. 102, dated September 8, 2000.
2/19/2001	Submitted information that was requested by FDA to initiate the Division of Scientific Investigations (DSI) consultation.
2/20/2001	Submitted findings of Dr. Delbado (France) (Protocol No. CSTI 571 B0202): subclavian vein thrombosis, upper limb edema and pain in limb.

2/21/2001	Submitted findings of Dr. Carole B. Miller (Protocol No. STI 571 0114): paresthesia NEC, pain in limb, disease progression NOS and drug ineffectiveness.
2/22/2001	Submitted findings of Dr. Carole B. Miller (Protocol No. STI 571 0114): paresthesia NEC, pain in limb, disease progression NOS and drug ineffectiveness. (Follow-up report)
2/26/2001	Received FAX from FDA containing comments and questions from the Clinical Pharmacology Reviewer on Serial No. 094, dated August 7, 2000.
2/26/2001	Sent FAX to FDA containing a 7-day Safety Report on the findings of Dr. Randy Brown (Protocol No. CSTI 571 0115): aggravated hepatitia and increased blood bilirubin.

NDA PERIOD

2/27/2001	Submitted NDA for "Glivec" capsules, which was assigned NDA Nos. 21-335, together with a request for priority review.
3/5/2001	Received handwritten note on FDA FAX, dated March 5, 2001, responding to the request for chemistry information in order to initiate inspection requests.
3/6/2001	Sent a copy of the cover letter detailing the information sent to the Division of Scientific Information as follow-ups to the Glivec submissions.
3/6/2001	In reference to a Novartis' letter, dated December 22, 2000, Section 2 (Reference No. 001-1401) was amended by replacing the proposed generic name with **imatinib** as selected by the WHO and the proposed tradename **Glivec** is under review.
3/7/2000	Received FDA LETTER acknowledging receipt of the new drug application for **Glivec (imatinib mesylate)** 50 mg and 100 mg capsules, submitted on February 27, 2001. This application has been designated priority review.
3/9/2001	Sent E-mail to, and received E-mail from, FDA regarding a corrupted file containing clinical data, discovered on Disk 1 of the Glivec NDA submitted on February 27, 2001. Replacement files will be provided.
3/9/2001	Submitted a disk containing replacement files for clinical data which substitute the files in the original NDA.

3/14/2001	In accordance with previous agreements, submitted amendment to provide a stability update for the drug product and updated drug substance documentation. Included was Three Months' Stability Results, STI 571, 100 mg capsules, dated March 12, 2001.
3/20/2001	Sent letter confirming the inspection readiness of the Novartis sites listed in the Glivec application, as requested by FDA at the March 16, 2001 NDA meeting.
3/21/2001	Requested approval to import the subject bulk product for Glivec (imatinib mesylate) capsules, 100 mg, in anticipation of an early approval and to assure launch supply.
3/26/2001	Received FAX from FDA requesting some clinical pharmacology information regarding *in vitro* studies and dissolution conditions.
3/29/2001	TELECONFERENCE with FDA to clarify requests from the Clinical Pharmacology Reviewers.
3/29/200	Received FAX from FDA with data listings for Protocol No. 102.
3/30/2001	Submitted minor amendment providing documentation of the USAN adopted name for the drug: **imatinib mesylate.**
3/30/2001	Submitted CMC amendment containing a previously agreed upon 12-month drug substance stability update. Also noted was a discrepancy in the documentation regarding the re-test period for the drug substance.
4/2/2001	Received FAX from FDA containing comments from the tradename consultant as to the reasons why "Glivec" is not approved for use.
4/2/2001	Received FAX from FDA containing a request from the Chemistry Reviewer for stability data from three drug substance batches.

4/3/2001	Received FAX from FDA containing a request from the Pharmcology/Toxicology Reviewer that the 39-day monkey study be submitted to the NDA in hard copy; desk copy to be submitted in electronic version. Also requested was the status of when the day-34 stability results for the 26-rat study will be submitted.
4/4/2001	Submitted CMC amendment containing the requested drug substance stability information requested in FDA FAX dated April 2, 2001.
4/5/2001	TELECONFERENCE with FDA concerning the submission of the 120-day Efficacy and Safety Report.
4/5/2001	TELECONFERENCE with FDA Clinical Pharmacology Reviewers to go over several outstanding questions received to date.
4/5/2001	Submitted non-clinical amendment containing the Final Report, entitled: "39-week oral gavage (b.i.d.) toxicity study in monkeys with a 4-week recovery period." (Study No. 007048) Also included was Amendment No. 1 to the Final Report, entitled: "26-week oral (gavage) toxicity study in rats with a 4-week recovery period." (Study No. 007033)
4/6/2001	Received FAX from FDA containing Medical Reviewer data tables so that Novartis may evaluate whether FDA has accurately interpreted the data. Explanations of the tables were provided.
4/10/2001	Submitted minor CMC amendment containing the response to the Clinical Pharmacology request on April 4, 2001.
4/12/2001	Sent letter authorizing the FDA to share certain information to specific foreign government regulatory health authorities for the purpose of reviewing the NDA registration application.

4/12/2001	Submitted amendment to a pending application providing minor corrections to the submitted population PK data files for Study Nos. 102, 109 and 110, as agreed upon in a teleconference on April 5, 2001.
4/13/2001	Submitted minor CMC amendment to a pending application containing the six-month drug substance stability commitment report and the 12-month long-term registration stability data for the remaining one batch of drug product.
4/19/2001	Submitted minor amendment providing for the removal of Novartis, East Hanover, as a site to perform stability testing.
4/24/2001	Submitted a revision to the letter of authorization for foreign government. The contact person for the cooperative review in Canada has changed.
4/24/2000	Submitted the full and complete Novartis response to CMC question received from the Agency on April 20, 2001.
4/26/2001	Received FAX from FDA suggesting changes in the Adverse Events section of the package insert.
4/30/2001	Submitted copies of draft promotional materials (Phase II website) to be used during the first 120 days of the post-approval period.
4/30/2001	Received FAX from FDA requesting two additional changes to the draft label.
5/1/2001	TELECONFERENCE with FDA to discuss comments/concerns by DDMAC on review of launch materials.

5/1/2001	Submitted revised bottle labels to address the CMC comment (fax dated April 20, 2001) and reflect the new tradename approved on April 17, 2001.
5/2/2001	Provided a draft courtesy copy of the Gleevec press release.
5/4/2001	Submitted minor amendment providing Novartis' agreement to comply with all of the Phase IV commitments referenced in a FDA FAX dated April 27, 2001.
5/4/2001	Submitted a complete response to FDA comments made during a May 3, 2001 teleconference. A six-month stability report was also included.
5/7/2001	Submitted an additional version of the Phase I website submitted on April 26, 2001. Also included was a proposed "fair balance" statement for DDMAC's review and comments.
5/8/2001	Submitted copies of draft promotional materials of revised ASCO panels originally submitted on April 23, 2001.
5/8/2001	Submitted minor amendment providing Novartis' updated agreement to comply with all of the Phase IV commitments, referenced in a FDA FAX dated April 27, 2001, and an E-mail dated May 8, 2001.
5/8/2001	Received an E-mail from FDA containing the Clinical Pharmacology Final Review comments.
5/9/2001	Submitted a revised press release, originally submitted on May 2, 2001, which better reflects the label changes in the Package Insert agreed upon with the Division.
5/10/2001	Received FDA LETTER approving NDA 21-335.